SERTRALINE HYDROCHLORIDE - sertraline hydrochloride tablet, film coated
Barr Laboratories Inc.

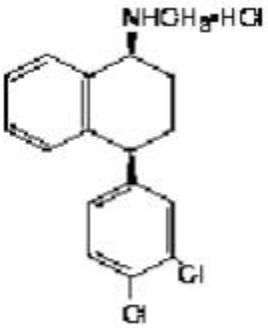
Rx Only

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of sertraline HCl or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Sertraline HCl tablets are not approved for the treatment of major depressive disorder in pediatric patients. (See Warnings and Precautions: Pediatric Use)
Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Sertraline hydrochloride is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It has a molecular weight of 342.7. Sertraline hydrochloride has the following chemical name: (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride. The empirical formula $C_{17}H_{17}NCl_2$•HCl is represented by the following structural formula:



Sertraline hydrochloride is a white crystalline powder that is slightly soluble in water and isopropyl alcohol, and sparingly soluble in ethanol.
Each tablet for oral administration contains sertraline hydrochloride equivalent to 25 mg, 50 mg or 100 mg of sertraline. In addition each tablet contains the following inactive ingredients: Colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, povidone, sodium citrate dihydrate and titanium dioxide. The 25 mg also contains FD&C Blue No. 2 and D&C Yellow No. 10. The 50 mg also contains FD&C Blue No. 2. The 100 mg also contains FD&C Yellow No. 6 and D&C Yellow No. 10.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Studies at clinically relevant doses in man have demonstrated that sertraline blocks the uptake of serotonin into human platelets. In vitro studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. In vitro studies have shown that sertraline has no significant affinity for adrenergic (alpha$_1$, alpha$_2$, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic ($5HT_{1A}$, $5HT_{1B}$, $5HT_2$), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs. The chronic administration of sertraline was found in animals to downregulate brain norepinephrine receptors, as has been observed with other drugs effective in the treatment of major depressive disorder. Sertraline does not inhibit monoamine oxidase.

Pharmacokinetics

Systemic Bioavailability– In man, following oral once-daily dosing over the range of 50 to 200 mg for 14 days, mean peak plasma concentrations (Cmax) of sertraline occurred between 4.5 to 8.4 hours post-dosing. The average terminal elimination half-life of plasma sertraline is about 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved

after approximately one week of once-daily dosing. Linear dose-proportional pharmacokinetics were demonstrated in a single dose study in which the Cmax and area under the plasma concentration time curve (AUC) of sertraline were proportional to dose over a range of 50 to 200 mg. Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation, compared to a single dose, of sertraline with repeated dosing over a 50 to 200 mg dose range. The single dose bioavailability of sertraline tablets is approximately equal to an equivalent dose of solution.

In a relative bioavailability study comparing the pharmacokinetics of 100 mg sertraline as the oral solution to a 100 mg sertraline tablet in 16 healthy adults, the solution to tablet ratio of geometric mean AUC and Cmax values were 114.8% and 120.6%, respectively. 90% confidence intervals (CI) were within the range of 80-125% with the exception of the upper 90% CI limit for Cmax which was 126.5%.

The effects of food on the bioavailability of the sertraline tablet and oral concentrate were studied in subjects administered a single dose with and without food. For the tablet, AUC was slightly increased when drug was administered with food but the Cmax was 25% greater, while the time to reach peak plasma concentration (Tmax) decreased from 8 hours post-dosing to 5.5 hours. For the oral concentrate, Tmax was slightly prolonged from 5.9 hours to 7.0 hours with food.

Metabolism– Sertraline undergoes extensive first pass metabolism. The principal initial pathway of metabolism for sertraline is N-demethylation. N-desmethylsertraline has a plasma terminal elimination half-life of 62 to 104 hours. Both *in vitro* biochemical and *in vivo* pharmacological testing have shown N-desmethylsertraline to be substantially less active than sertraline. Both sertraline and N-desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation. In a study of radio-labeled sertraline involving two healthy male subjects, sertraline accounted for less than 5% of the plasma radioactivity. About 40-45% of the administered radioactivity was recovered in urine in 9 days. Unchanged sertraline was not detectable in the urine. For the same period, about 40-45% of the administered radio activity was accounted for in feces, including 12-14% unchanged sertraline.

Desmethylsertraline exhibits time-related, dose dependent increases in AUC (0-24 hour), Cmax and Cmin, with about a 5-9 fold increase in these pharmacokinetic parameters between day 1 and day 14.

Protein Binding–In vitro protein binding studies performed with radiolabeled 3H-sertraline showed that sertraline is highly bound to serum proteins (98%) in the range of 20 to 500 ng/mL. However, at up to 300 and 200 ng/mL concentrations, respectively, sertraline and N-desmethylsertraline did not alter the plasma protein binding of two other highly protein bound drugs, viz., warfarin and propranolol (see PRECAUTIONS).

Pediatric Pharmacokinetics– Sertraline pharmacokinetics were evaluated in a group of 61 pediatric patients (29 aged 6-12 years, 32 aged 13-17 years) with a DSM-III-R diagnosis of major depressive disorder. Patients included both males (N=28) and females (N=33). During 42 days of chronic sertraline dosing, sertraline was titrated up to 200 mg/day and maintained at that dose for a minimum of 11 days. On the final day of sertraline 200 mg/day, the 6-12 year old group exhibited a mean sertraline AUC (0-24 hr) of 3107 ng-hr/mL, mean Cmax of 165 ng/mL, and mean half-life of 26.2 hr. The 13-17 year old group exhibited a mean sertraline AUC (0-24 hr) of 2296 ng-hr/mL, mean Cmax of 123 ng/mL, and mean half-life of 27.8 hr. Higher plasma levels in the 6-12 year old group were largely attributable to patients with lower body weights. No gender associated differences were observed. By comparison, a group of 22 separately studied adults between 18 and 45 years of age (11 male, 11 female) received 30 days of 200 mg/day sertraline and exhibited a mean sertraline AUC (0-24 hr) of 2570 ng-hr/mL, mean Cmax of 142 ng/mL, and mean half-life of 27.2 hr. Relative to the adults, both the 6-12 year olds and the 13-17 year olds showed about 22% lower AUC (0-24 hr) and Cmax values when plasma concentration was adjusted for weight. These data suggest that pediatric patients metabolize sertraline with slightly greater efficiency than adults. Nevertheless, lower doses may be advisable for pediatric patients given their lower body weights, especially in very young patients, in order to avoid excessive plasma levels (see DOSAGE AND ADMINISTRATION).

Age– Sertraline plasma clearance in a group of 16 (8 male, 8 female) elderly patients treated for 14 days at a dose of 100 mg/day was approximately 40% lower than in a similarly studied group of younger (25 to 32 y.o.) individuals. Steady-state, therefore, should be achieved after 2 to 3 weeks in older patients. The same study showed a decreased clearance of desmethylsertraline in older males, but not in older females.

Liver Disease– As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of sertraline. In patients with chronic mild liver impairment (N=10, 8 patients with Child-Pugh scores of 5-6 and 2 patients with Child-Pugh scores of 7-8) who received 50 mg sertraline per day maintained for 21 days, sertraline clearance was reduced, resulting in approximately 3-fold greater exposure compared to age-matched volunteers with no hepatic impairment (N=10). The exposure to desmethylsertraline was approximately 2-fold greater compared to age-matched volunteers with no hepatic impairment. There were no significant differences in plasma protein binding observed between the two groups. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The results suggest that the use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Disease – Sertraline is extensively metabolized and excretion of unchanged drug in urine is a minor route of elimination. In volunteers with mild to moderate (CLcr=30-60 mL/min), moderate to severe (CLcr=10-29 mL/min) or severe (receiving hemodialysis) renal impairment (N=10 each group), the pharmacokinetics and protein binding of 200 mg sertraline per day maintained for 21 days were not altered compared to age-matched volunteers (N=12) with no renal impairment. Thus sertraline multiple dose pharmacokinetics appear to be unaffected by renal impairment (see PRECAUTIONS).

Clinical Trials

Major Depressive Disorder– The efficacy of sertraline HCl as a treatment for major depressive disorder was established in two placebo-controlled studies in adult outpatients meeting DSM-III criteria for major depressive disorder. Study 1 was an 8-week study with flexible dosing of sertraline HCl in a range of 50 to 200 mg/day; the mean dose for completers was 145 mg/day. Study 2 was a 6-week fixed-dose study, including sertraline HCl doses of 50, 100, and 200 mg/day. Overall, these studies demonstrated sertraline HCl to be superior to placebo on the Hamilton Depression Rating Scale and the Clinical Global Impression Severity and Improvement scales. Study 2 was not readily interpretable regarding a dose response relationship for effectiveness.

Study 3 involved depressed outpatients who had responded by the end of an initial 8-week open treatment phase on sertraline HCl 50-200 mg/day. These patients (N=295) were randomized to continuation for 44 weeks on double-blind sertraline HCl 50-200 mg/day or placebo. A statistically significantly lower relapse rate was observed for patients taking sertraline HCl compared to those on placebo. The mean dose for completers was 70 mg/day.

Analyses for gender effects on outcome did not suggest any differential responsiveness on the basis of sex.

INDICATIONS AND USAGE

Major Depressive Disorder– Sertraline HCl is indicated for the treatment of major depressive disorder in adults.

The efficacy of sertraline HCl in the treatment of a major depressive episode was established in six to eight week controlled trials of adult outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see Clinical Trials under CLINICAL PHARMACOLOGY).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant action of sertraline HCl in hospitalized depressed patients has not been adequately studied.

The efficacy of sertraline HCl in maintaining an antidepressant response for up to 44 weeks following 8 weeks of open-label acute treatment (52 weeks total) was demonstrated in a placebo-controlled trial. The usefulness of the drug in patients receiving sertraline HCl for extended periods should be reevaluated periodically (see Clinical Trials under CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS). Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

Sertraline HCl is contraindicated in patients with a hypersensitivity to sertraline or any of the inactive ingredients in sertraline HCl.

WARNINGS

Cases of serious sometimes fatal reactions have been reported in patients receiving sertraline hydrochloride, a selective serotonin reuptake inhibitor (SSRI), in combination with a monoamine oxidase inhibitor (MAOI). Symptoms of a drug interaction between an SSRI and an MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability, and extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued an SSRI and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, sertraline HCl should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping sertraline HCl before starting an MAOI.

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive-compulsive disorder and social anxiety disorder) as well.**No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times

of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION —Discontinuation of Treatment with sertraline, for a description of the risks of discontinuation of sertraline).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for sertraline should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that sertraline is not approved for use in treating bipolar depression.

PRECAUTIONS

General

Activation of Mania/Hypomania– During premarketing testing, hypomania or mania occurred in approximately 0.4% of sertraline HCl treated patients.

Weight Loss– Significant weight loss may be an undesirable result of treatment with sertraline for some patients, but on average, patients in controlled trials had minimal, 1 to 2 pound weight loss, versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss.

Seizure– Sertraline HCl has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarket testing. No seizures were observed among approximately 3000 patients treated with sertraline HCl in the development program for major depressive disorder. However, 4 patients out of approximately 1800 (220 <18 years of age) exposed during the development program for another disorder experienced seizures, representing a crude incidence of 0.2%. Three of these patients were adolescents, two with a seizure disorder and one with a family history of seizure disorder, none of whom were receiving anticonvulsant medication. Accordingly, sertraline HCl should be introduced with care in patients with a seizure disorder.

Discontinuation of Treatment with Sertraline HCl

During marketing of sertraline HCl and other SSRIs and SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g. paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with sertraline HCl. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

Abnormal Bleeding
Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a non-selective nonsteroidal anti-inflammatory drug (i.e., NSAIDs that inhibit both cyclooxygenase isoenzymes, COX 1 and 2) or aspirin potentiated the risk of bleeding (see DRUG INTERACTIONS). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of sertraline HCl with non-selective NSAIDs (i.e., NSAIDs that inhibit both cyclooxygenase isoenzymes, COX 1 and 2), aspirin, or other drugs that affect coagulation.

Weak Uricosuric Effect– Sertraline HCl is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown.

Use in Patients with Concomitant Illness– Clinical experience with sertraline HCl in patients with certain concomitant systemic illness is limited. Caution is advisable in using sertraline HCl in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Patients with a recent history of myocardial infarction or unstable heart disease were excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 774 patients who received sertraline HCl in double-blind trials were evaluated and the data indicate that sertraline HCl is not associated with the development of significant ECG abnormalities.

Sertraline HCl administered in a flexible dose range of 50 to 200 mg/day (mean dose of 89 mg/day) was evaluated in a post-marketing, placebo-controlled trial of 372 randomized subjects with a DSM-IV diagnosis of major depressive disorder and recent history of myocardial infarction or unstable angina requiring hospitalization. Exclusions from this trial included, among others, patients with uncontrolled hypertension, need for cardiac surgery, history of CABG within 3 months of index event, severe or symptomatic bradycardia, non-atherosclerotic cause of angina, clinically significant renal impairment (creatinine > 2.5 mg/dl), and clinically significant hepatic dysfunction. Sertraline HCl treatment initiated during the acute phase of recovery (within 30 days post-MI or post-hospitalization for unstable angina) was indistinguishable from placebo in this study on the following week 16 treatment endpoints: left ventricular ejection fraction, total cardiovascular events (angina, chest pain, edema, palpitations, syncope, postural dizziness, CHF, MI, tachycardia, bradycardia, and changes in BP), and major cardiovascular events involving death or requiring hospitalization (for MI, CHF, stroke, or angina).

Sertraline HCl is extensively metabolized by the liver. In patients with chronic mild liver impairment, sertraline clearance was reduced, resulting in increased AUC, Cmax and elimination half-life. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Since sertraline HCl is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. A clinical study comparing sertraline pharmacokinetics in healthy volunteers to that in patients with renal impairment ranging from mild to severe (requiring dialysis) indicated that the pharmacokinetics and protein binding are unaffected by renal disease. Based on the pharmacokinetic results, there is no need for dosage adjustment in patients with renal impairment (see CLINICAL PHARMACOLOGY).

Interference with Cognitive and Motor Performance– In controlled studies, sertraline HCl did not cause sedation and did not interfere with psychomotor performance. (See Information for Patients.)

Hyponatremia– Several cases of hyponatremia have been reported and appeared to be reversible when sertraline HCl was discontinued. Some cases were possibly due to the syndrome of inappropriate anti-diuretic hormone secretion. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Platelet Function– There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking sertraline HCl. While there have been reports of abnormal bleeding or purpura in several patients taking sertraline HCl, it is unclear whether sertraline HCl had a causative role.

Information for Patients
Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with sertraline HCl and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for sertraline. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should

be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.
Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking sertraline.
Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during anti-depressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.
Patients should be told that although sertraline has not been shown to impair the ability of normal subjects to perform tasks requiring complex motor and mental skills in laboratory experiments, drugs that act upon the central nervous system may affect some individuals adversely. Therefore, patients should be told that until they learn how they respond to sertraline they should be careful doing activities when they need to be alert, such as driving a car or operating machinery.
Patients should be cautioned about the concomitant use of sertraline and non-selective NSAIDs (i.e., NSAIDs that inhibit both cyclooxygenase isoenzymes, COX 1 and 2), aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.
Patients should be told that although sertraline has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of sertraline and alcohol is not advised.
Patients should be told that while no adverse interaction of sertraline with over-the-counter (OTC) drug products is known to occur, the potential for interaction exists. Thus, the use of any OTC product should be initiated cautiously according to the directions of use given for the OTC product.
Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.
Patients should be advised to notify their physician if they are breast feeding an infant.

Laboratory Tests
None.

Drug Interactions
Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins– Because sertraline is tightly bound to plasma protein, the administration of sertraline HCl to a patient taking another drug which is tightly bound to protein (e.g., warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound sertraline HCl by other tightly bound drugs.
In a study comparing prothrombin time AUC (0-120 hr) following dosing with warfarin (0.75 mg/kg) before and after 21 days of dosing with either sertraline HCl (50-200 mg/day) or placebo, there was a mean increase in prothrombin time of 8% relative to baseline for sertraline HCl compared to a 1% decrease for placebo ($p<0.02$). The normalization of prothrombin time for the sertraline HCl group was delayed compared to the placebo group. The clinical significance of this change is unknown. Accordingly, prothrombin time should be carefully monitored when sertraline HCl therapy is initiated or stopped.
Cimetidine– In a study assessing disposition of sertraline HCl (100 mg) on the second of 8 days of cimetidine administration (800 mg daily), there were significant increases in sertraline HCl mean AUC (50%), Cmax (24%) and half-life (26%) compared to the placebo group. The clinical significance of these changes is unknown.
CNS Active Drugs– In a study comparing the disposition of intravenously administered diazepam before and after 21 days of dosing with either sertraline HCl (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the sertraline HCl group compared to a 19% decrease relative to baseline for the placebo group ($p<0.03$). There was a 23% increase in Tmax for desmethyldiazepam in the sertraline HCl group compared to a 20% decrease in the placebo group ($p<0.03$). The clinical significance of these changes is unknown.
In a placebo-controlled trial in normal volunteers, the administration of two doses of sertraline HCl did not significantly alter steady-state lithium levels or the renal clearance of lithium.
Nonetheless, at this time, it is recommended that plasma lithium levels be monitored following initiation of sertraline HCl therapy with appropriate adjustments to the lithium dose.
In a controlled study of a single dose (2 mg) of pimozide, 200 mg sertraline (q.d.) coadministration to steady state was associated with a mean increase in pimozide AUC and Cmax of about 40%, but was not associated with any changes in EKG. Since the highest recommended pimozide dose (10 mg) has not been evaluated in combination with sertraline, the effect on QT interval and PK parameters at doses higher than 2 mg at this time are not known. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide and due to the interaction noted at a low dose of pimozide, concomitant administration of sertraline HCl and pimozide should be contraindicated (see CONTRAINDICATIONS).
Results of a placebo-controlled trial in normal volunteers suggest that chronic administration of sertraline 200 mg/day does not produce clinically important inhibition of phenytoin metabolism. Nonetheless, at this time, it is recommended that plasma phenytoin

concentrations be monitored following initiation of sertraline therapy with appropriate adjustments to the phenytoin dose, particularly in patients with multiple underlying medical conditions and/or those receiving multiple concomitant medications.

The effect of sertraline on valproate levels has not been evaluated in clinical trials. In the absence of such data, it is recommended that plasma valproate levels be monitored following initiation of sertraline therapy with appropriate adjustments to the valproate dose.

The risk of using sertraline HCl in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of sertraline HCl and such drugs is required.

There is limited controlled experience regarding the optimal timing of switching from other drugs effective in the treatment of major depressive disorder. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents. The duration of an appropriate washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established.

Monoamine Oxidase Inhibitors– See CONTRAINDICATIONS and WARNINGS.

Drugs Metabolized by P450 3A4– In three separate *in vivo* interaction studies, sertraline was coadministered with cytochrome P450 3A4 substrates, terfenadine, carbamazepine, or cisapride under steady-state conditions. The results of these studies indicated that sertraline did not increase plasma concentrations of terfenadine, carbamazepine, or cisapride. These data indicate that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance. Results of the interaction study with cisapride indicate that sertraline 200 mg (q.d.) induces the metabolism of cisapride (cisapride AUC and Cmax were reduced by about 35%).

Drugs Metabolized by P450 2D6– Many drugs effective in the treatment of major depressive disorder, e.g., the SSRIs, including sertraline, and most tricyclic antidepressant drugs effective in the treatment of major depressive disorder inhibit the biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase), and, thus, may increase the plasma concentrations of coadministered drugs that are metabolized by P450 2D6. The drugs for which this potential interaction is of greatest concern are those metabolized primarily by 2D6 and which have a narrow therapeutic index, e.g., the tricyclic antidepressant drugs effective in the treatment of major depressive disorder and the Type 1C antiarrhythmics propafenone and flecainide. The extent to which this interaction is an important clinical problem depends on the extent of the inhibition of P450 2D6 by the antidepressant and the therapeutic index of the coadministered drug. There is variability among the drugs effective in the treatment of major depressive disorder in the extent of clinically important 2D6 inhibition, and in fact sertraline at lower doses has a less prominent inhibitory effect on 2D6 than some others in the class. Nevertheless, even sertraline has the potential for clinically important 2D6 inhibition. Consequently, concomitant use of a drug metabolized by P450 2D6 with sertraline HCl may require lower doses than usually prescribed for the other drug. Furthermore, whenever sertraline HCl is withdrawn from co-therapy, an increased dose of the coadministered drug may be required (see Tricyclic Antidepressant Drugs Effective in the Treatment of Major Depressive Disorder under PRECAUTIONS).

Sumatriptan– There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.

Tricyclic Antidepressant Drugs Effective in the Treatment of Major Depressive Disorder (TCAs)– The extent to which SSRI–TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with sertraline HCl, because sertraline may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is coadministered with sertraline HCl (see Drugs Metabolized by P450 2D6 under PRECAUTIONS).

Hypoglycemic Drugs– In a placebo-controlled trial in normal volunteers, administration of sertraline HCl for 22 days (including 200 mg/day for the final 13 days) caused a statistically significant 16% decrease from baseline in the clearance of tolbutamide following an intravenous 1000 mg dose. Sertraline HCl administration did not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug. The clinical significance of this decrease in tolbutamide clearance is unknown.

Atenolol– Sertraline HCl (100 mg) when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol.

Digoxin– In a placebo-controlled trial in normal volunteers, administration of sertraline HCl for 17 days (including 200 mg/day for the last 10 days) did not change serum digoxin levels or digoxin renal clearance.

Microsomal Enzyme Induction– Preclinical studies have shown sertraline HCl to induce hepatic microsomal enzymes. In clinical studies, sertraline HCl was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in antipyrine half-life following administration of 200 mg/day for 21 days. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism.

Drugs That Interfere With Hemostasis (Non-selective NSAIDs, Aspirin, Warfarin, etc.) Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between the use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of a non-selective NSAID (i.e., NSAIDs that inhibit both cyclooxygenase isoenzymes, COX 1 and 2) or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with sertraline HCl.

Electroconvulsive Therapy– There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and sertraline HCl.

Alcohol– Although sertraline HCl did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of sertraline HCl and alcohol is not recommended.

Carcinogenesis– Lifetime carcinogenicity studies were carried out in CD-1 mice and Long-Evans rats at doses up to 40 mg/kg/day. These doses correspond to 1 times (mice) and 2 times (rats) the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was a dose-related increase of liver adenomas in male mice receiving sertraline at 10-40 mg/kg (0.25-1.0 times the MRHD on a mg/m^2 basis). No increase was seen in female mice or in rats of either sex receiving the same treatments, nor was there an increase in hepatocellular carcinomas. Liver adenomas have a variable rate of spontaneous occurrence in the CD-1 mouse and are of unknown significance to humans. There was an increase in follicular adenomas of the thyroid in female rats receiving sertraline at 40 mg/kg (2 times the MRHD on a mg/m^2 basis); this was not accompanied by thyroid hyperplasia. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10-40 mg/kg (0.5-2.0 times the MRHD on a mg/m^2 basis) compared to placebo controls, this effect was not clearly drug related.

Mutagenesis– Sertraline had no genotoxic effects, with or without metabolic activation, based on the following assays: bacterial mutation assay; mouse lymphoma mutation assay; and tests for cytogenetic aberrations in vivo in mouse bone marrow and in vitro in human lymphocytes.

Impairment of Fertility– A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (4 times the maximum recommended human dose on a mg/m^2 basis).

Pregnancy-Pregnancy Category C– Reproduction studies have been performed in rats and rabbits at doses up to 80 mg/kg/day and 40 mg/kg/day, respectively. These doses correspond to approximately 4 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was no evidence of teratogenicity at any dose level. When pregnant rats and rabbits were given sertraline during the period of organogenesis, delayed ossification was observed in fetuses at doses of 10 mg/kg (0.5 times the MRHD on a mg/m^2 basis) in rats and 40 mg/kg (4 times the MRHD on a mg/m^2 basis) in rabbits. When female rats received sertraline during the last third of gestation and throughout lactation, there was an increase in the number of stillborn pups and in the number of pups dying during the first 4 days after birth. Pup body weights were also decreased during the first four days after birth. These effects occurred at a dose of 20 mg/kg (1 times the MRHD on a mg/m^2 basis). The no effect dose for rat pup mortality was 10 mg/kg (0.5 times the MRHD on a mg/m^2 basis). The decrease in pup survival was shown to be due to in utero exposure to sertraline. The clinical significance of these effects is unknown. There are no adequate and well-controlled studies in pregnant women. Sertraline HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy-Nonteratogenic Effects– Neonates exposed to sertraline HCl and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. These findings are based on postmarketing reports. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS).

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1,000 live births in the general population and is associated with substantial noenatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk. When treating a pregnant woman with sertraline HCl during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic in the context of antidepressant therapy at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

Labor and Delivery– The effect of sertraline HCl on labor and delivery in humans is unknown.

Nursing Mothers– It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sertraline HCl is administered to a nursing woman.

Pediatric Use– Safety and effectiveness in pediatric patients with major depressive disorder have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Two placebo controlled trials (n=373) in pediatric patients with MDD have been conducted with sertraline, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of sertraline hydrochloride tablets in a child or adolescent must balance the potential risks with the clinical need. Sertraline pharmacokinetics were evaluated in 61 pediatric patients between 6 and 17 years of age and revealed similar drug exposures to those of adults when plasma concentration was adjusted for weight (see Pharmacokinetics under CLINICAL PHARMACOLOGY).

Approximately 600 pediatric patients between 6 and 17 years of age have received sertraline in clinical trials, both controlled and uncontrolled. The adverse event profile observed in these patients was generally similar to that observed in adult studies with sertraline (see ADVERSE REACTIONS). As with other SSRIs, decreased appetite and weight loss have been observed in association with the use of sertraline. In a pooled analysis of two 10 week, double-blind, placebo-controlled, flexible dose (50-200 mg) outpatient trials for major depressive disorder (n=373), there was a difference in weight change between sertraline and placebo of roughly 1 kilogram, for both children (ages 6-11) and adolescents (ages 12-17), in both cases representing a slight weight loss for sertraline compared to a slight gain for placebo. At baseline the mean weight for children was 39.0 kg for sertraline and 38.5 kg for placebo. At baseline the mean weight for adolescents was 61.4 kg for sertraline and 62.5 kg for placebo. There was a bigger difference between sertraline and placebo in the proportion of outliers for clinically important weight loss in children than in adolescents. For children, about 7% had a weight loss > 7% of body weight compared to none of the placebo patients; for adolescents, about 2% had a weight loss > 7% of body weight compared to about 1% of the placebo patients. A subset of these patients who completed the randomized controlled trials (sertraline n=99, placebo n=122) were continued into a 24-week, flexible-dose, open-label, extension study. A mean weight loss of approximately 0.5 kg was seen during the first eight weeks of treatment for subjects with first exposure to sertraline during the open-label extension study, similar to mean weight loss observed among sertraline treated subjects during the first eight weeks of the randomized controlled trials. The subjects continuing in the open label study began gaining weight compared to baseline by week 12 of sertraline treatment. Those subjects who completed 34 weeks of sertraline treatment (10 weeks in a placebo controlled trial + 24 weeks open label, n=68) had weight gain that was similar to that expected using data from age-adjusted peers. Regular monitoring of weight and growth is recommended if treatment of a pediatric patient with an SSRI is to be continued long term. Safety and effectiveness in pediatric patients with major depressive disorder have not been established.

The risks, if any, that may be associated with sertraline's use beyond 1 year in children and adolescents have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that sertraline is safe for use in children and adolescents derives from clinical studies that were 10 to 52 weeks in duration and from the extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long-term sertraline use on the growth, development, and maturation of children and adolescents. Although there is no affirmative finding to suggest that sertraline possesses a capacity to adversely affect growth, development or maturation, the absence of such findings is not compelling evidence of the absence of the potential of sertraline to have adverse effects in chronic use (see **WARNINGS – Clinical Worsening and Suicide Risk**).

Geriatric Use– U.S. geriatric clinical studies of sertraline HCl in major depressive disorder included 663 sertraline HCl-treated subjects ≥ 65 years of age, of those, 180 were ≥ 75 years of age. No overall differences in the pattern of adverse reactions were observed in the geriatric clinical trial subjects relative to those reported in younger subjects (see ADVERSE REACTIONS), and other reported experience has not identified differences in safety patterns between the elderly and younger subjects. As with all medications, greater sensitivity of some older individuals cannot be ruled out. There were 947 subjects in placebo-controlled geriatric clinical studies of sertraline HCl in major depressive disorder. No overall differences in the pattern of efficacy were observed in the geriatric clinical trial subjects relative to those reported in younger subjects.

Other Adverse Events in Geriatric Patients. In 354 geriatric subjects treated with sertraline HCl in placebo-controlled trials, the overall profile of adverse events was generally similar to that shown in Table 1. Urinary tract infection was the only adverse event not appearing in Table 1 and reported at an incidence of at least 2% and at a rate greater than placebo in placebo-controlled trials.

As with other SSRIs, sertraline HCl has been associated with cases of clinically significant hyponatremia in elderly patients (see Hyponatremia under PRECAUTIONS).

ADVERSE REACTIONS

During its premarketing assessment, multiple doses of sertraline HCl were administered to over 4000 adult subjects as of February 18, 2000. The conditions and duration of exposure to sertraline HCl varied greatly, and included (in overlapping categories) clinical pharmacology studies, open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and studies for multiple indications, including major depressive disorder.

Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of sertraline HCl who experienced a treatment-emergent adverse event of the type cited on at least one occasion while receiving sertraline HCl. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Incidence in Placebo-Controlled Trials– Table 1 enumerates the most common treatment-emergent adverse events associated with the use of sertraline HCl (incidence of at least 5% for sertraline HCl and at least twice that for placebo within at least one of the

indications) for the treatment of adult patients with major depressive disorder/other* in placebo-controlled clinical trials. Most patients in major depressive disorder/other* studies, received doses of 50 to 200 mg/day.

TABLE 1 MOST COMMON TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

	Percentage of Patients Reporting Event Major Depressive Disorder/Other*	
Body System/Adverse Event	**Sertraline HCl (N=861)**	**Placebo (N=853)**
Autonomic Nervous System Disorders		
Ejaculation Failure (1)	7	<1
Mouth Dry	16	9
Sweating Increased	8	3
Centr. & Periph. Nerv. System Disorders		
Somnolence	13	6
Tremor	11	3
Dizziness	12	7
General		
Fatigue	11	8
Pain	1	2
Malaise	<1	1
Gastrointestinal Disorders		
Abdominal Pain	2	2
Anorexia	3	2
Constipation	8	6
Diarrhea/Loose Stools	18	9
Dyspepsia	6	3
Nausea	26	12
Psychiatric Disorders		
Agitation	6	4
Insomnia	16	9
Libido Decreased	1	<1

(1) Primarily ejaculatory delay. Denominator used was for male patients only (N=271 sertraline HCl major depressive disorder/other*; N=271 placebo major depressive disorder/other*).
*Major depressive disorder and other premarketing controlled trials.

Associated with Discontinuation in Placebo-Controlled Clinical Trials

Table 2 lists the adverse events associated with discontinuation of sertraline HCl treatment (incidence at least twice that for placebo and at least 1% for sertraline HCl in clinical trials) in major depressive disorder/other*.

TABLE 2 MOST COMMON ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION IN PLACEBO-CONTROLLED CLINICAL TRIALS

Adverse Event	**Major Depressive Disorder/Other (N=861)**
Abdominal Pain	–
Agitation	1%
Anxiety	–
Diarrhea/Loose Stools	2%
Dizziness	–
Dry Mouth	1%

Dyspepsia	–
Ejaculation Failure (1)	1%
Fatigue	–
Headache	2%
Hot Flushes	–
Insomnia	1%
Nausea	4%
Nervousness	–
Palpitation	–
Somnolense	1%
Tremor	2%

(1) Primarily ejaculatory delay. Denominator used was for male patients only (N=271 major depressive disorder/other*).
*Major depressive disorder and other premarketing controlled trials.

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

Table 3 below displays the incidence of sexual side effects reported by at least 2% of patients taking sertraline HCl in placebo-controlled trials.

TABLE 3

Adverse Event	Sertraline HCl	Placebo
Ejaculation failure* (primarily delayed ejaculation)	14%	1%
Decreased libido**	6%	1%

*Denominator used was for male patients only (N=1118 sertraline HCl; N=926 placebo)
**Denominator used was for male and female patients (N=2799 sertraline HCl; N=2394 placebo)

There are no adequate and well-controlled studies examining sexual dysfunction with sertraline treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Other Adverse Events in Pediatric Patients– In over 600 pediatric patients treated with sertraline HCl, the overall profile of adverse events was generally similar to that seen in adult studies. However, the following adverse events, from controlled trials, not appearing in Table 1, were reported at an incidence of at least 2% and occurred at a rate of at least twice the placebo rate (N=281 patients treated with sertraline HCl): fever, hyperkinesia, urinary incontinence, aggressive reaction, sinusitis, epistaxis and purpura.

Other Events Observed During the Premarketing Evaluation of Sertraline HCl– Following is a list of treatment-emergent adverse events reported during premarketing assessment of sertraline HCl in clinical trials (over 4000 adult subjects) except those already listed in the previous tables or elsewhere in labeling.

In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of sertraline HCl who experienced an event of the type cited on at least one occasion while receiving sertraline HCl. All events are included except those already listed in the previous tables or elsewhere in labeling and those reported in terms so general as to be uninformative and those for which a causal relationship to sertraline HCl treatment seemed remote. It is important to emphasize that although the events reported occurred during treatment with sertraline HCl, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to

1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

Autonomic Nervous System Disorders–*Frequent*: impotence; *Infrequent*: flushing, increased saliva, cold clammy skin, mydriasis; *Rare*: pallor, glaucoma, priapism, vasodilation.

Body as a Whole–*General Disorders–Rare*: allergic reaction, allergy.

Cardiovascular–*Frequent*: palpitations, chest pain; *Infrequent*: hypertension, tachycardia, postural dizziness, postural hypotension, periorbital edema, peripheral edema, hypotension, peripheral ischemia, syncope, edema, dependent edema; *Rare*: precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, cerebrovascular disorder.

Central and Peripheral Nervous System Disorders–*Frequent*: hypertonia, hypoesthesia; *Infrequent*: twitching, confusion, hyperkinesia, vertigo, ataxia, migraine, abnormal coordination, hyperesthesia, leg cramps, abnormal gait, nystagmus, hypokinesia; *Rare*: dysphonia, coma, dyskinesia, hypotonia, ptosis, choreoathetosis, hyporeflexia.

Disorders of Skin and Appendages– *Infrequent*: pruritus, acne, urticaria, alopecia, dry skin, erythematous rash, photosensitivity reaction, maculopapular rash; *Rare*: follicular rash, eczema, dermatitis, contact dermatitis, bullous eruption, hypertrichosis, skin discoloration, pustular rash.

Endocrine Disorders–*Rare*: exophthalmos, gynecomastia.

Gastrointestinal Disorders–*Frequent*: appetite increased; *Infrequent*: dysphagia, tooth caries aggravated, eructation, esophagitis, gastroenteritis; *Rare*: melena, glossitis, gum hyperplasia, hiccup, stomatitis, tenesmus, colitis, diverticulitis, fecal incontinence, gastritis, rectum hemorrhage, hemorrhagic peptic ulcer, proctitis, ulcerative stomatitis, tongue edema, tongue ulceration.

General–*Frequent*: back pain, asthenia, malaise, weight increase; *Infrequent*: fever, rigors, generalized edema; *Rare*: face edema, aphthous stomatitis.

Hearing and Vestibular Disorders–*Rare*: hyperacusis, labyrinthine disorder.

Hematopoietic and Lymphatic–*Rare*: anemia, anterior chamber eye hemorrhage.

Liver and Biliary System Disorders–*Rare*: abnormal hepatic function.

Metabolic and Nutritional Disorders–*Infrequent*: thirst; *Rare*: hypoglycemia, hypoglycemia reaction.

Musculoskeletal System Disorders–*Frequent*: myalgia; *Infrequent*: arthralgia, dystonia, arthrosis, muscle cramps, muscle weakness.

Psychiatric Disorders–*Frequent*: yawning, other male sexual dysfunction, other female sexual dysfunction; *Infrequent*: depression, amnesia, paroniria, teeth-grinding, emotional lability, apathy, abnormal dreams, euphoria, paranoid reaction, hallucination, aggressive reaction, aggravated depression, delusions; *Rare*: withdrawal syndrome, suicide ideation, libido increased, somnambulism, illusion.

Reproductive–*Infrequent*: menstrual disorder, dysmenorrhea, intermenstrual bleeding, vaginal hemorrhage, amenorrhea, leukorrhea; *Rare*: female breast pain, menorrhagia, balanoposthitis, breast enlargement, atrophic vaginitis, acute female mastitis.

Respiratory System Disorders–*Frequent*: rhinitis; *Infrequent*: coughing, dyspnea, upper respiratory tract infection, epistaxis, bronchospasm, sinusitis; *Rare*: hyperventilation, bradypnea, stridor, apnea, bronchitis, hemoptysis, hypoventilation, laryngismus, laryngitis.

Special Senses–*Frequent*: tinnitus; *Infrequent*: conjunctivitis, earache, eye pain, abnormal accommodation; *Rare*: xerophthalmia, photophobia, diplopia, abnormal lacrimation, scotoma, visual field defect.

Urinary System Disorders–*Infrequent*: micturition frequency, polyuria, urinary retention, dysuria, nocturia, urinary incontinence; *Rare*: cystitis, oliguria, pyelonephritis, hematuria, renal pain, strangury.

Laboratory Tests– In man, asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%) in association with sertraline HCl administration. These hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation.

Sertraline HCl therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%), and a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance.

Other Events Observed During the Postmarketing Evaluation of Sertraline HCl– Reports of adverse events temporally associated with sertraline HCl that have been received since market introduction, that are not listed above and that may have no causal relationship with the drug, include the following: acute renal failure, anaphylactoid reaction, angioedema, blindness, optic neuritis, cataract, increased coagulation times, bradycardia, AV block, atrial arrhythmias, QT-interval prolongation, ventricular tachycardia (including torsade de pointes-type arrhythmias), hypothyroidism, agranulocytosis, aplastic anemia and pancytopenia, leukopenia, thrombocytopenia, lupus-like syndrome, serum sickness, hyperglycemia, galactorrhea, hyperprolactinemia, neuroleptic malignant syndrome-like events, extrapyramidal symptoms, oculogyric crisis, serotonin syndrome, psychosis, pulmonary hypertension, severe skin reactions, which potentially can be fatal, such as Stevens-Johnson syndrome, vasculitis, photosensitivity and other severe cutaneous disorders, rare reports of pancreatitis, and liver events—clinical features (which in the majority of cases appeared to be reversible with discontinuation of sertraline HCl) occurring in one or more patients include: elevated enzymes, increased bilirubin, hepatomegaly, hepatitis, jaundice, abdominal pain, vomiting, liver failure and death.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class– Sertraline HCl is not a controlled substance.

Physical and Psychological Dependence– In a placebo-controlled, double-blind, randomized study of the comparative abuse liability of sertraline HCl, alprazolam, and d-amphetamine in humans, sertraline HCl did not produce the positive subjective effects indicative of abuse potential, such as euphoria or drug liking, that were observed with the other two drugs. Premarketing clinical experience with sertraline HCl did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. In animal studies sertraline HCl

does not demonstrate stimulant or barbiturate-like (depressant) abuse potential. As with any CNS active drug, however, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of sertraline HCl misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience– Of 1,027 cases of overdose involving sertraline hydrochloride worldwide, alone or with other drugs, there were 72 deaths (circa 1999).

Among 634 overdoses in which sertraline hydrochloride was the only drug ingested, 8 resulted in fatal outcome, 75 completely recovered, and 27 patients experienced sequelae after overdosage to include alopecia, decreased libido, diarrhea, ejaculation disorder, fatigue, insomnia, somnolence and serotonin syndrome. The remaining 524 cases had an unknown outcome. The most common signs and symptoms associated with non-fatal sertraline hydrochloride overdosage were somnolence, vomiting, tachycardia, nausea, dizziness, agitation and tremor.

The largest known ingestion was 13.5 grams in a patient who took sertraline hydrochloride alone and subsequently recovered. However, another patient who took 2.5 grams of sertraline hydrochloride alone experienced a fatal outcome.

Other important adverse events reported with sertraline hydrochloride overdose (single or multiple drugs) include bradycardia, bundle branch block, coma, convulsions, delirium, hallucinations, hypertension, hypotension, manic reaction, pancreatitis, QT-interval prolongation, serotonin syndrome, stupor and syncope.

Overdose Management– Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for sertraline are known.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR®).

DOSAGE AND ADMINISTRATION

Initial Treatment

Dosage for Adults

Major Depressive Disorder– Sertraline HCl treatment should be administered at a dose of 50 mg once daily.

While a relationship between dose and effect has not been established for major depressive disorder, patients were dosed in a range of 50-200 mg/day in the clinical trials demonstrating the effectiveness of sertraline HCl for the treatment of this indication. Consequently, a dose of 50 mg, administered once daily, is recommended as the initial therapeutic dose. Patients not responding to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24 hour elimination half-life of sertraline HCl, dose changes should not occur at intervals of less than 1 week.

Maintenance/Continuation/Extended Treatment

Major Depressive Disorder – It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy beyond response to the acute episode. Systematic evaluation of sertraline HCl has demonstrated that its antidepressant efficacy is maintained for periods of up to 44 weeks following 8 weeks of initial treatment at a dose of 50-200 mg/day (mean dose of 70 mg/day) (see Clinical Trials under CLINICAL PHARMACOLOGY). It is not known whether the dose of sertraline HCl needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment.

Switching Patients to or from a Monoamine Oxidase Inhibitor– At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with sertraline HCl. In addition, at least 14 days should be allowed after stopping sertraline HCl before starting an MAOI (see CONTRAINDICATIONS and WARNINGS).

Special Populations

Dosage for Hepatically Impaired Patients– The use of sertraline in patients with liver disease should be approached with caution. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Treatment of Pregnant Women During the Third Trimester– Neonates exposed to sertraline HCl and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with sertraline HCl during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering sertraline HCl in the third trimester.

Discontinuation of Treatment with Sertraline HCl
Symptoms associated with discontinuation of sertraline HCl and other SSRIs and SNRIs, have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

HOW SUPPLIED
Sertraline hydrochloride equivalent to 25 mg, 50 mg or 100 mg of sertraline.
25 mg – Light green, round, scored on one side, film coated tablets in bottles of 30, 50, 100, 500 and 1000.
Debossed: PLIVA on one side and 930 on the other side.
50 mg – Light blue, round, scored on one side, film coated tablets in bottles of 30, 100, 500, 1000 and 5000.
Debossed: PLIVA on one side and 931 on the other side.
100 mg – Light yellow, round, scored on one side, film coated tablets in bottles of 30, 100, 500 and 1000.
Debossed: PLIVA on one side and 932 on the other side.
Store at 20°-25°C (68°-77°F)[See USP Controlled Room Temperature].

Medication Guide
About Using Antidepressants in Children and Teenagers
What is the most important information I should know if my child is being prescribed an antidepressant?
Parents or guardians need to think about 4 important things when their child is prescribed an anti-depressant:
1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions
Children and teenagers sometimes think about suicide, and many report trying to kill themselves.
Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal*.
A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. **No one committed suicide in these studies**, but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.
For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with
• Bipolar illness (sometimes called manic-depressive illness)

• A family history of bipolar illness

• A personal or family history of attempting suicide

If any of these are present, make sure you tell your healthcare provider before your child takes an antidepressant.
2. How to Try to Prevent Suicidal Thoughts and Actions
To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.
Whenever an antidepressant is started or its dose is changed, pay close attention to your child.
After starting an antidepressant, your child should generally see his or her healthcare provider:
• Once a week for the first 4 weeks

• Every 2 weeks for the next 4 weeks

• After taking the antidepressant for 12 weeks

• After 12 weeks, follow your healthcare provider's advice about how often to come back

• More often if problems or questions arise (see Section 3)

You should call your child's healthcare provider between visits if needed.
3. You Should Watch for Certain Signs If Your Child is Taking an Antidepressant

Contact your child's healthcare provider***right away*** if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her healthcare provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®) has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®), sertraline (Zoloft®), fluvoxamine, and clomipramine (Anafranil®).

Your healthcare provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your healthcare provider or pharmacist where to find more information.

*Prozac® is a registered trademark of Eli Lilly and Company

*Zoloft® is a registered trademark of Pfizer Pharmaceuticals

*Anafranil® is a registered trademark of Mallinckrodt Inc.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

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